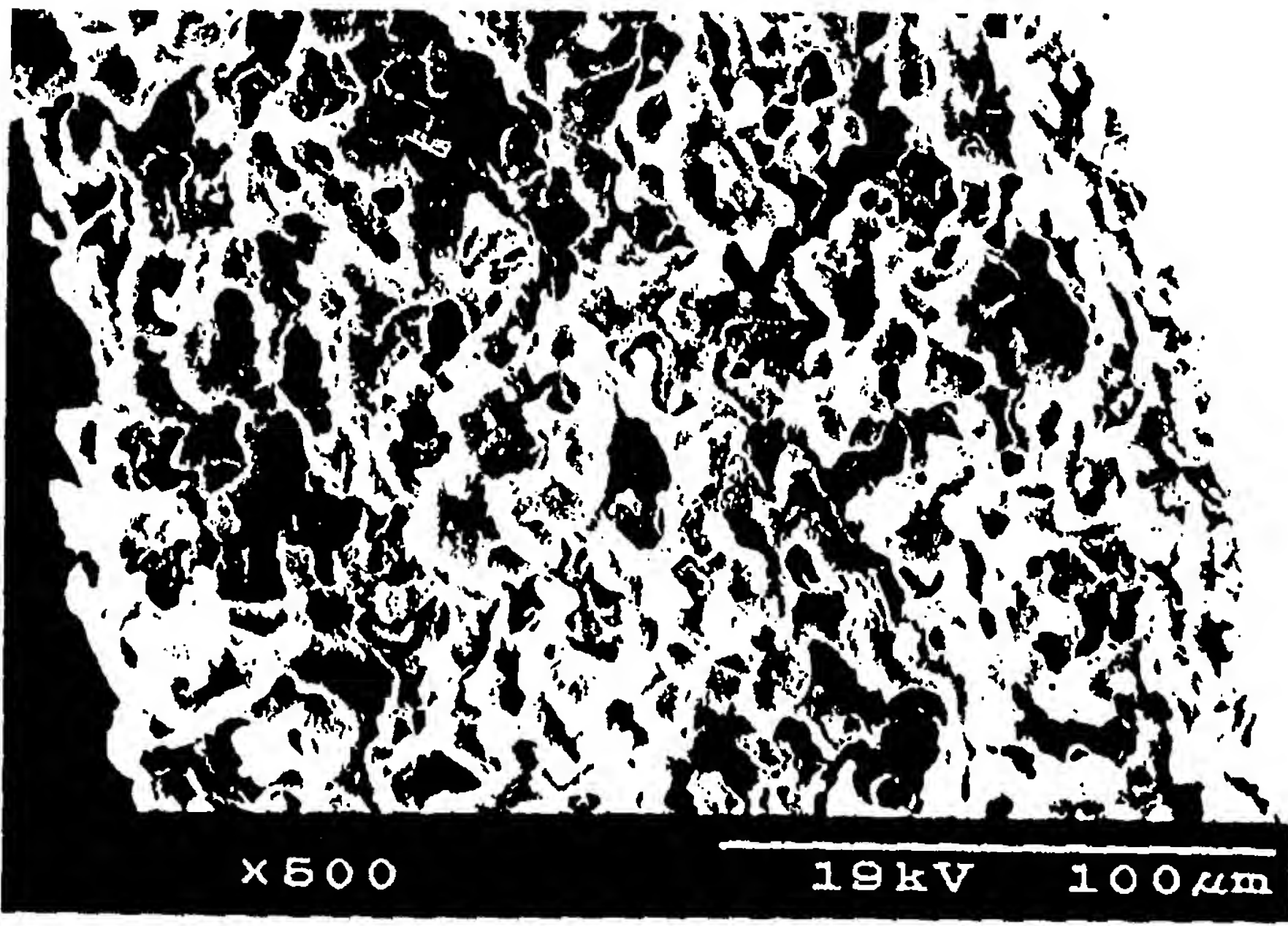


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(21) International Application Number: PCT/KR97/00289 (22) International Filing Date: 31 December 1997 (31.12.97) (30) Priority Data: 1996/82443 31 December 1996 (31.12.96) KR (71) Applicant (for all designated States except US): KOREA INSTITUTE OF SCIENCE AND TECHNOLOGY [KR/KR]; 39-1, Hawolgok-dong, Sungbook-ku, Seoul 139-791 (KR). (72) Inventors; and (75) Inventors/Applicants (for US only): JEONG, Seo, Young [KR/KR]; Life Apartment 205-501, 5, Munchonmaeul, Juyeop 2-dong, Ilsan-ku, Koyang, Kyungki-do 411-372 (KR). CHOI, Kuiwon [KR/KR]; Kist Apartment 9832, 39-1, Hawolgok-dong, Sungbook-ku, Seoul 136-791 (KR). KWON, Ick-Chan [KR/KR]; Shiyong Apartment 706-704, 274, Hakye-dong, Nowon-ku, Seoul 139-230 (KR). KIM, Yong-Hee [KR/KR]; Hyundai Apartment 54-503, 462, Apkujong-dong, Kangnam-ku, Seoul 135-111 (KR). CHOI, Jae, Bong [KR/KR]; Kist Apartment 9351, 39-1, Hawolgok-dong, Sungbook-ku, Seoul 136-791 (KR). LEE, Kyu, Back [KR/KR]; Hanshin Apartment 115-604, 616-100, Donnam-dong, Sungbook-ku, Seoul 136-060 (KR).		(74) Agent: PARK, Jang, Won; Park, Kim & Partner, 200, Nonhyun-dong, Kangnam-ku, Seoul 135-010 (KR). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>With amended claims and statement.</i>
(54) Title: METHOD OF MANUFACTURING POROUS MATRIX-TYPE CONTROLLED RELEASE SYSTEMS USING EMULSION TECHNIQUE		
(57) Abstract <p>A method of manufacturing a porous matrix-type drug delivery system is provided. It comprises the steps of: dispersing, stirring, and emulsifying an aqueous solution of a drug in an organic solvent having a polymer compound and a surface active agent solved therein; thereafter forming it into a desirable matrix shape; lyophilizing or drying it at a low temperature or room temperature until the matrix surface is hardened; and drying it again in order to remove the water and the organic solvent.</p> <div data-bbox="666 1642 1845 2499"></div>		

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**METHOD OF MANUFACTURING POROUS MATRIX-TYPE
CONTROLLED RELEASE SYSTEMS USING EMULSION TECHNIQUE**

TECHNICAL FIELD

5 The present invention relates to a new method of preparing a matrix-type drug delivery system that allows a controlled-release of drugs, and which has various porosity. The system is manufactured by evaporating solvents from the matrix that is formed from an emulsion solution. The emulsion is made by emulsifying an aqueous solution containing a
10 water-soluble drug in a polymer-dissolved organic solution using a surface-active agent.

BACKGROUND ART

 Emulsion is a stable dispersion of one liquid in a second immiscible
15 liquid, and typically, a surface-active agent is used in order to maintain the emulsion state.

 The controlled-release is a characteristic that is capable of improving effects of medical usage, and of reducing its side-effects by making the drugs
20 to be released from the drug-containing substance according to a time schedule. Matrix system means that the drug is evenly or unevenly dissolved or dispersed inside a matrix, in which the matrix substance is continuously aligned.

25 The release of a water-soluble drug from a non-biodegradable matrix, or from a biodegradable matrix having a low degradation rate typically follows first-order release kinetics, and its release rate decreases gradually as time passes. [Higuchi T., J. Pharm. Sci. 50, 874 ~ 875 (1961), Higuchi T., Pharm. Sci, 52, 1145 ~ 1149 (1963), Manduit et al, J. controlled Release. 25, 43 ~ 49
30 (1993)]. In general, the water-soluble drug cannot pass through the hydrophobic matrix. When a water-soluble drug is loaded in a hydrophobic

polymer matrix below a percolation threshold, only the drug exposed on its surface is released at an initial period, while most of the drug still remains in the matrix even after a long time has passed. When the water-soluble drug is loaded above the percolation threshold, its release rate depends on the solubility of the drug in the body fluids, and on the diffusion of the drug through the water channels generated by the drug dissolution after the drug is in contact with body fluids. Therefore, in the system loaded with a low molecular compound having a high solubility, a large quantity of initial burst and fast release of the drug are shown. [Siegel et al, J. Controlled Release, 8,223 ~ 236 (1989), Saltzman et al, J. Biophys., 55, 163 ~ 171 (1989)].

In the case of a system in which a water-soluble drug of high osmotic activity is dispersed inside the water-insoluble polymer matrix, the water-soluble drug exposed on the surface is rapidly dissolved so as to form water-channels and is released at the initial period. The portion of the drug away from the water-channels functions as an osmotic pressure-causing material across the wall of the polymer matrix which functions as pseudo-semipermeable membrane. The osmotic pressure gradually breaks the polymer matrix from an outermost to an inside, and the drug is released in a controlled fashion. [Amsden et al, J. Controlled Release. 30, 45 ~ 56 (1994), Amsden BG and Cheng Y., J. Controlled Release, 31,21 ~ 32 (1994)]. Therefore, a drug that causes a high osmotic pressure can be released in a controlled-release fashion, and the remaining drug can be released even if in a case that the drug is loaded below the percolation threshold.

25

However, when the polymer matrix surrounding the drug is too thick, the possibility of breaking the polymer matrix wall is very low, and the rate of water passing through the polymer down to the drug is decreased, so that the release of the drug is very poor, and the more drug remains in the matrix. [Zhang et al, J. Pharm, Pharmacol. 46, 718 ~ 724 (1994), Amsden BG and Cheng Y., J. Controlled Release, 31, 21 ~ 32 (1994)]

30

To load a water-soluble drug on a hydrophobic matrix, either simple dispersion of drug particles in an organic polymer solution, or extrusion or compression of the drug-polymer mixture in a solid phase is used. Those loading methods do not allow the even distribution of the drug inside the
5 matrix so that the rate change of the drug release is uneven as time passes.

DISCLOSURE OF THE INVENTION

A method of manufacturing a porous matrix-type drug delivery system according to the present invention comprises the steps of: dispersing, stirring,
10 and emulsifying an aqueous solution containing a water-soluble drug in an organic solvent in which a polymer compound and a surface active agent are dissolved therein; thereafter forming the resultant into a desirable matrix shape; lyophilizing or drying at a low temperature or at a room temperature until the matrix surface is hardened ; and drying again to remove water and
15 organic solvents.

The porous matrix-type controlled-release system of the present invention is a matrix substance for oral or non-oral administration of drugs, and can be widely and efficiently used as medical treatment agents because
20 the drugs can be released at a constant rate in a determined period.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will become more fully understood from the detailed description given hereinbelow and the accompanying drawings which
25 are given by way of illustration only, and thus are not limitative of the present invention, and wherein:

Figure 1 shows a SEM (Scanning Electron Microscope) image of a cross-sectional view of a poly-L-lactide film containing 20 wt % of gentamycin
30 according to a porous matrix-type controlled-release system of the present invention before release;

Figure 2 shows a SEM image of a sectional view of a poly-L-lactide film containing 20 wt % of gentamycin according to porous matrix-type controlled-release system of the present invention after release;

5 Figure 3 is a graph showing an early release vs. time relation of a porous matrix-type controlled-release system according to the present invention;

10 Figure 4 is a zero-order release graph of the long term release vs. time relation of a porous matrix-type controlled-release system according to the present invention;

15 Figure 5 is a release graph of a porous matrix-type controlled-release system of the present invention according to a change in the concentration of span 80;

20 Figure 6 shows a SEM image of a cross-sectional view of a poly-L-lactide film containing 10 wt % of cefotaxime sodium according to a porous matrix-type controlled-release system of the present invention;

Figure 7 is a drug release graph of polylactide-co-glycolide film and poly-D,L-lactide film containing 20 wt % of gentamycin sulphate according to a porous matrix-type controlled-release system of the present invention ; and

25 Figure 8 shows a cross-sectional SEM view of a ethylene-vinylacetate copolymer film containing 20 wt % of gentamycin sulphate according to a porous matrix-type controlled-release system of the present invention.

MODES FOR CARRYING OUT THE PREFERRED EMBODIMENTS

30 The present invention is directed to provide a method of dispersing a water-soluble drug evenly into a hydrophobic polymer matrix by an emulsion

method by using an oil-soluble surface active agent. The present invention is also directed to provide a method of manufacturing porous matrix-type controlled-release system containing an osmotically active, water-soluble drug which is released by an induced osmotic pressure across a
5 pseudo-semipermeable polymer matrix and/or a surface active substance. The present invention has the following outstanding advantages:

1. Constant release rate of drug;
2. Controllable release rate of drug; and,
- 10 3. Very low residual drug.

Due to a high porosity, most of the drug contained therein is released and a low osmotic pressure is needed to break the matrix wall surrounding the drug.

15

To achieve the above objective and in accordance with the purposes of the present invention as embodied and described, a method of manufacturing a porous matrix-type drug delivery system is provided. The system is constructed in such a manner that an aqueous solution containing
20 a water-soluble drug is dispersed and stirred to be emulsified in an organic solution that contains a polymer compound and a surface active agent. After forming it to a desired matrix shape, the emulsion is lyophilized immediately or dried at room temperatures (16 to 30° C) for a predetermined time (which can vary depending on the boiling point of the organic solution used) until the
25 surface of the matrix is hardened. After the drying, vacuum-drying (below 0.75mmHg) is performed to remove organic solvents and water.

The polymer compounds which can be used as the matrix of the present invention are polylactide, lactide-glycolide copolymer, silicone rubber,
30 ethylene-vinyl acetate copolymer, polyortho-ester copolymer, etc. Especially polylactide, lactide-glycolide polymer is suitable because it is widely used as

biocompatible and biodegradable materials, as in the case of raw materials for suture materials. The polylactide used in this invention is a homopolymer having an average molecular weight of 100,000 (Polyscience. Inc of U.S., example 1,2,3), and the lactide-glycolide copolymer is Resomer RG858
5 (Boehringer Ingelheim of Germany, example 4). Ethylene-vinylacetate copolymer (Aldrich Chemical Company, Inc. of U.S. its vinyl-acetate is 33 %, example 5), which does not decompose but its biocompatibility is excellent, is used.

10 The surface-active agent of the present invention can be selected from a group consisting of fat-acid, olefin, alkylcarbonyl, silicon elastomer, sulfate ester, petty alcohol sulfate, sulfate pete and oil, sulfonic acid-base, fat sulfonate, alkylaryl sulfonate, ligmin sulfonate, phosphoric acid ester, polyoxyethylene, polyoxyethylene caster oil, polyglycerol, polyol, imidazol,
15 altanolamine, hetamine, sulfobecamine, phosphotide, polyoxyethylene-sorbitan fat acid ester (Tween), sorbitan ester (Span), etc. and preferably, sorbitan monooleate (Span 80) of a sorbitan ester. Its concentration is preferable to be 0.1 to 5 wt % for the emulsion solution. The release rate of the drug, that is, drug release amount per time is changed
20 depending on the kind and density of the surface active agent (example 2). The usage of the surface active agent is limited to above, wherein the emulsion is difficult to achieve below those density, and above those density, the release rate is too slow, and side-effects may occur in clinical applications.

25 A variety of drugs can be used in the present invention. These include analgesics, anti-inflammatory agents, vermicide, cardiovascular drugs, urological drugs, antibiotic agents, anticoagulating agents, antidepressant, diabetes treatment agents, antiepileptic agents, antihypertensive agents, antifebrile, hormones, antiasthmatic agents, bronchodilators, diuretics,
30 digestive agents, sedatives, hypnotics, anesthetics, nutritional and tonic agents, antiseptic agents, preservation agents, stabilization agents,

insecticide, disinfectant, muscle-relaxant, antituberculosis and antileprosy agents, vaccines, etc. Although it depends on the therapeutic concentration of the drug, water-soluble drugs where the solubility of which is over 1mg/ml is preferable. When the solubility is low, the maximum drug loading
5 achievable by the present invention is too small.

As the organic solvents of the present invention, butyl alcohol, chloroform, cyclohexan, dichlorometan, dichloroethan, ethylacetate, ethylether, dipropylether, toluene, etc. can be used.

10

The volume ratio of the aqueous solution and the organic solvent is preferable to be 1:2 ~ 1:40. The initial burst of the drug can be increased by increasing the volume ratio of the aqueous solution. The reason why the range of the volume ratio is set is that the high volume ratio of the solutions makes
15 the emulsion formation difficult, and even when the emulsion is formed, the initial release amount of drug is too high. The shape of the matrix can be manufactured variously depending on the purpose, such as film, surface coating, pellet, tablet, plate, rod, etc.

20 The emulsification can be achieved by using well-known tools such as stirrer, vortex mixer, homogenizer, ultrasonic device, microfluidizer, etc.

Reference will now be made in detail to the preferred embodiments of the present invention, but the substitutions and alterations can be made
25 hereto without departing from the spirit and scope of the invention as defined by the claims.

Example 1

A 50% aqueous gentamycin solution was poured into a polymer
30 solution of dichloromethan having 16 % of poly-L-lactide (weight averaged molecular weight of 100,000), and 3% of span 80 (wt%). The weight of

gentamycin was 20 % of the weight of poly-L-lactide. The mixture solution was evenly emulsified by using a vortex mixer, a stirrer and a sonicator. The emulsion was cast on a clean glass plate and the thickness was adjusted by using an applicator of 1 mm height. It was dried at room temperatures for 4
5 hrs. and then vacuum-dried for 24 hrs. to form a solid film. SEM pictures of the film were taken before and after the release of the drug. The porosity of the film was determined by the amount of water included in the emulsion. (Fig. 1 and 2)

10 Drug release embodiment

Except for the change of gentamycin concentration of the aqueous solution in example 1 to 25%, 35%, 50%, the films were manufactured in the same manner as example 1. The films were cut into same sizes, and the release rate was measured by immersing the films in PBS of pH 7.4.

15

Comparative example 1 : initial release

The initial release of drug was increased with the increase of the water amount in the emulsion. (Fig.3)

20 Comparative example 2 : 0-order release for long term

After the period of initial release, zero-order release is maintained for a long-time. (Fig.4)

Example 2

25 Except for the change of gentamycin concentration of the aqueous solution in example 1 into 35%, and the change of span 80 concentration into 0.5%, 1%, 1.5%, 3%, the films were manufactured in the same way as example 1. The films were cut into same sizes and the drug was released in PBS of pH 7.4. The initial burst and release rate of the drugs were changed
30 depending on the concentration of the span 80. (Fig.5)

Example 3

A 10% aqueous cefotaxime sodium solution was poured into a polymer solution of methylene chloride having 16 wt% of poly-L-lactid (average molecular weight of 100,000), and 1 wt% of span 80. The weight of the cefotaxime sodium was 20wt% of the weight of lactide-glycolide copolymer. The mixture solution was evenly emulsified by using a vortex mixer, a stirrer and a sonicator. The emulsion was cast on a clean glass plate and the thickness was adjusted by using an applicator of 1 mm height. It was dried at room temperatures for 4 hrs. and then was vacuum-dried for 24 hrs. to form a solid film. SEM pictures of the film were taken before and after the release of the drug. The porosity of the film was determined by the amount of water included in the emulsion. (Fig. 6)

Example 4

A 35wt% aqueous gentamycin sulfate solution was put into a polymer solution of chloroform having 16 wt% of lactide-glycolide copolymer (Resomer RG858, Boehringer Ingelheim, Germany) and 1 wt % of span 80 or into a polymer solution of chloroform having 16 wt % of poly-D,L-lactid (Resomer R207, Boehringer Ingelheim, Germany), and 1 wt % of span 80. The weight of gentamycin sulfate was 20 % of the weight of polymers. The mixture solution was evenly emulsified by using a vortex mixer, a stirrer and a sonicator. The emulsion was cast on a clean glass plate and the thickness was adjusted by using an applicator of 1 mm height. It was dried at room temperatures for 4 hrs. and then was vacuum-dried for 24 hrs. to form a solid film. The films were cut into same sizes and the drug was released in PBS of pH 7.4. The drug was also released in a controlled fashion even when using the lactide-glycolide copolymer or poly-D,L-lactide. Especially, the release rate of poly-D,L-lactide film was faster than that of poly-L-lactide film. (Fig.7)

Example 5

A 35 wt% aqueous gentamycin sulfate solution was put into a polymer

solution of chloroform having 20 wt% of ethylene-vinylacetate copolymer (weight averaged molecular amount 130,000, ethylene: vinylacetate = 67: 33), and 1 wt% of span 80. The weight of gentamycin sulfate was 20% of the weight of ethylene vinylacetate copolymer. The mixture solution was evenly
5 emulsified by using a vortex mixer, a stirrer and a sonicator. The emulsion was cast on a clean glass plate and the thickness was adjusted by using an applicator of 1 mm height. It was dried at room temperatures for 4 hrs. and then vacuum-dried for 24 hrs. to form a solid film. SEM pictures of the film were taken before and after the release of the drug. The porosity of the film
10 was determined by the amount of water included in the emulsion. (Fig. 8)

CLAIMS

1. A method of manufacturing a porous matrix substance comprising the steps of:
dispersing, stirring, and emulsifying an aqueous solution containing a
5 drug in an organic solvent in which a polymer compound and a surface active agent are dissolved therein;
thereafter forming the resultant into a desirable matrix shape;
lyophilizing or drying at a low temperature or room temperature until the matrix surface is hardened; and,
10 drying again to remove water and the organic solvent.
2. The method as claimed in claim 1, wherein the polymer compound is selected from a group consisting of polylactides and lactide-glycolide copolymers.
15
3. The method as claimed in claim 1, wherein the surface-active agent is a sorbitan ester (Span).
4. The method as claimed in claim 1, wherein the drug is a
20 water-soluble drug for oral and non-oral administration that is dissolved in an inner aqueous solution inside an emulsion.
5. The method as claimed in claim 1, wherein the organic solvent is selected from a group consisting of dichloromethane and chloroform.
25
6. The method as claimed in claim 1, wherein the volume ratio of the aqueous solution to the organic solvent is 1:2 ~ 1:40.
7. The method as claimed in claim 1, wherein the addition amount
30 of the surface active agent is 0.1 ~ 5 wt % of the organic solvent.

AMENDED CLAIMS

[received by the International Bureau on 03 June 1998 (03.06.98);
original claims 1-5 amended; remaining claims unchanged (2 pages)]

1. A method of manufacturing a porous matrix substance comprising the steps of:
dispersing, stirring, and emulsifying an aqueous solution containing a
5 drug in an organic solvent in which a polymer compound and a surface active agent are dissolved in a water-in-oil type emulsion;
thereafter forming the resultant into a desirable matrix shape;
lyophilizing or drying at a low temperature or room temperature until the matrix surface is hardened; and,
10 drying again to remove water and the organic solvent.
2. The method as claimed in claim 1, wherein the polymer compound is selected from the group comprising of poly(L-lactide), poly(DL-lactide), polyglycolide, lactide-glycolide copolymers, poly ortho-ester
15 copolymers, ethylene-vinyl acetate copolymers, and ethylene-vinyl alcohol copolymers.
3. The method as claimed in claim 1, wherein the surface-active agent is selected from the comprising of sorbitan ester (Span) series and
20 Tween series.
4. The method as claimed in claim 1, wherein the drug is a water-soluble drug for oral and non-oral administration that is dissolved in an inner aqueous solution inside the water-in-oil type emulsion.
25
5. The method as claimed in claim 1, wherein the organic solvent is selected from the group comprising of dichloromethane and chloroform.
6. The method as claimed in claim 1, wherein the volume ratio of
30 the aqueous solution to the organic solvent is 1:2 ~ 1:40.

7. The method as claimed in claim 1, wherein the addition amount of the surface active agent is 0.1 ~ 5 wt % of the organic solvent.

Statement under Article 19

This application contains seven (7) claims, currently claims 1-7 are pending in this application. The International Search Report cited five documents as relevant to the present application: two documents were cited in the "A" category, one in the "Y" category", one in the "X" category, and one document was cited in both the "X" and "Y" categories.

In view of cited reference US 4,818,542 (cited in the "Y" category), claims 1 and 4 are amended to distinguish the present invention over the cited reference. Both the present invention and US 4,818,542 use an emulsion technique, however, the present invention uses an oil-in-water (W/O) type. In the present invention, the water phase contains pharmaceutical drugs, and the oil phase contains polymeric materials. An emulsion drop (water phase) is dispersed in a continuous phase of an organic solvent (oil phase). The whole system, i.e., the emulsion drops and the continuous phase, becomes a porous matrix (film shape) by step-wise drying.

In US 4,818,542, there is disclosed an emulsion drop which contains drugs and polymers shaped into a microsphere by precipitation or freeze drying.

Accordingly, it is believed the amendments to the claims will distinguish the present claims from the cited references.

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FIG.1

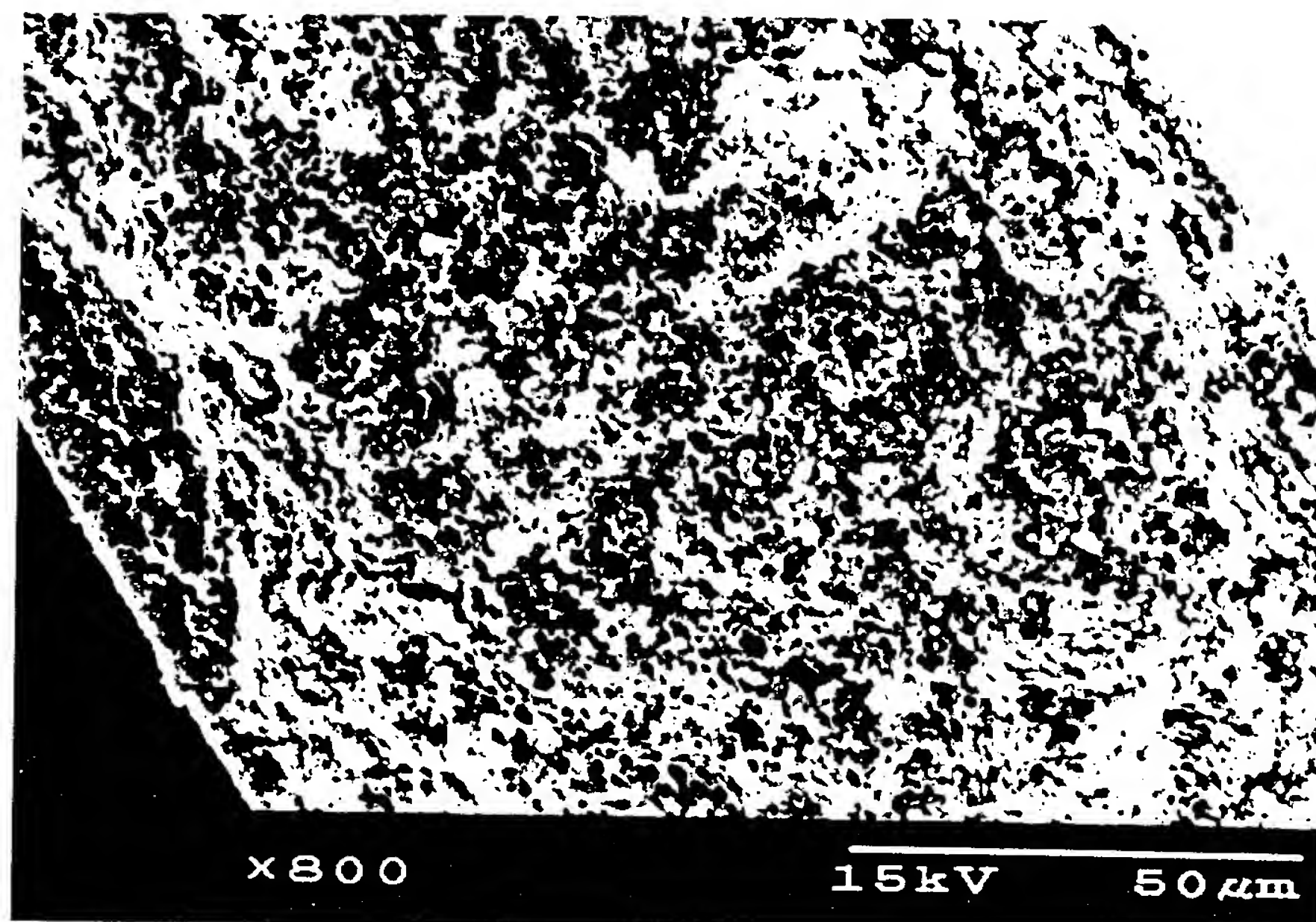


FIG.2

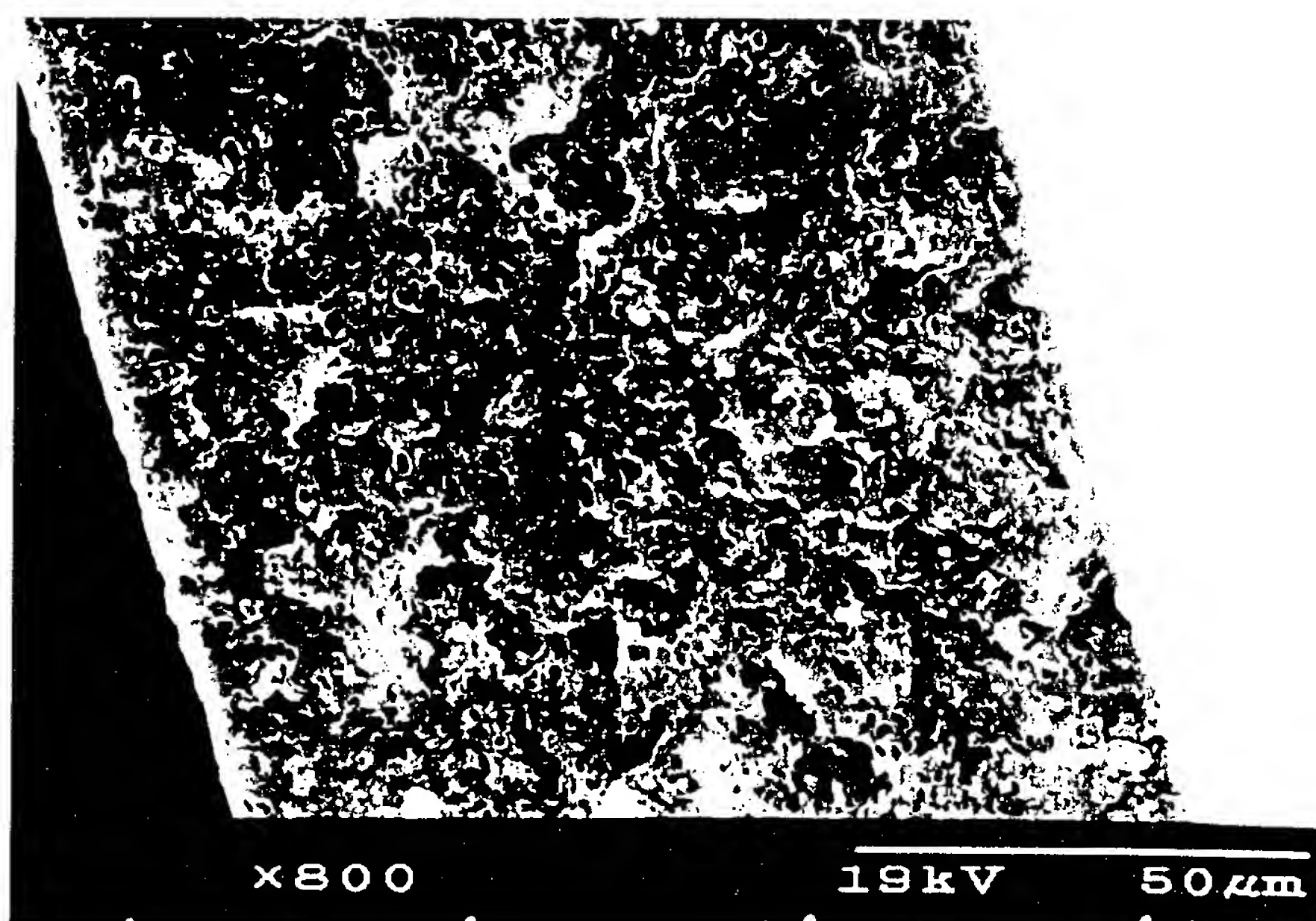


FIG.3

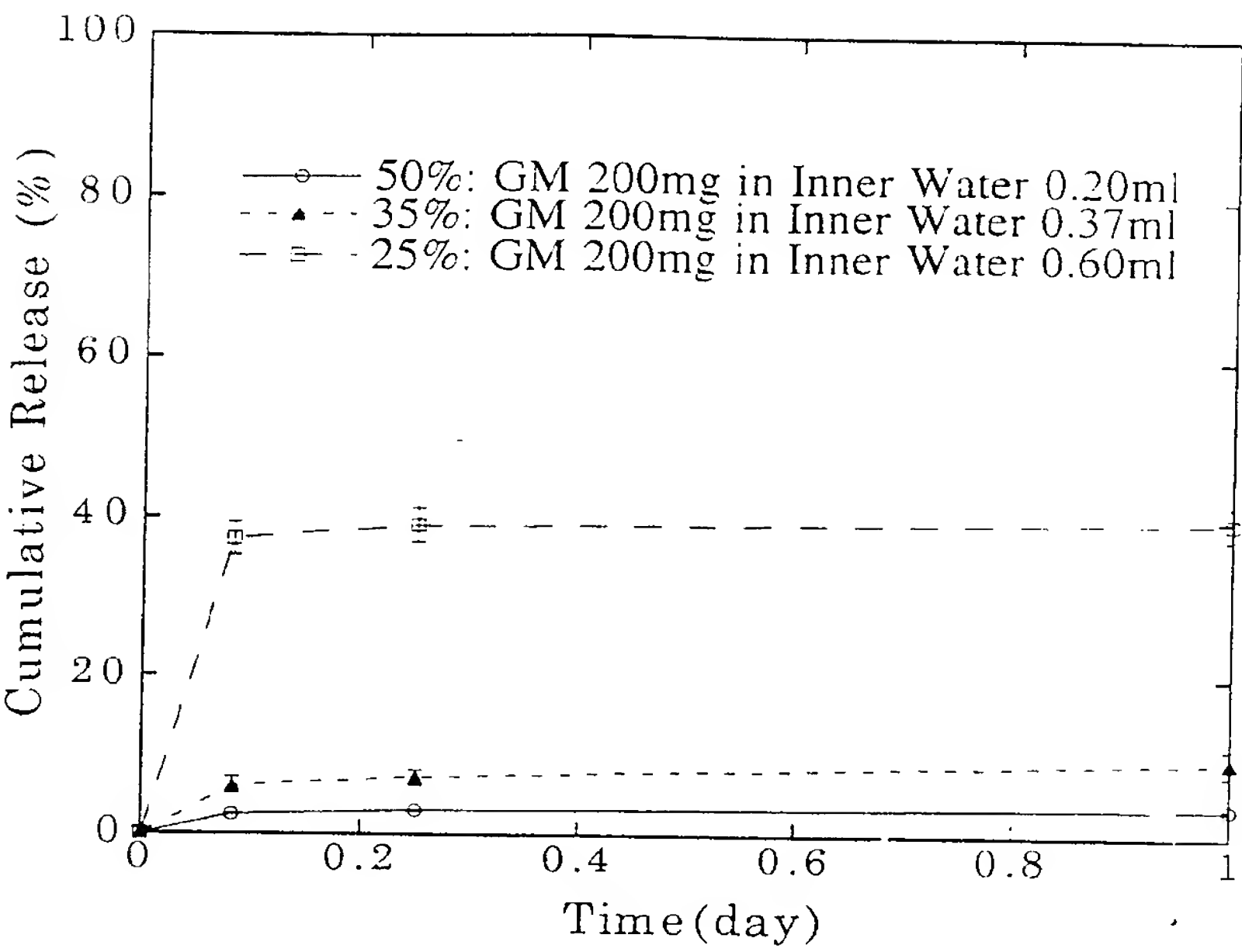
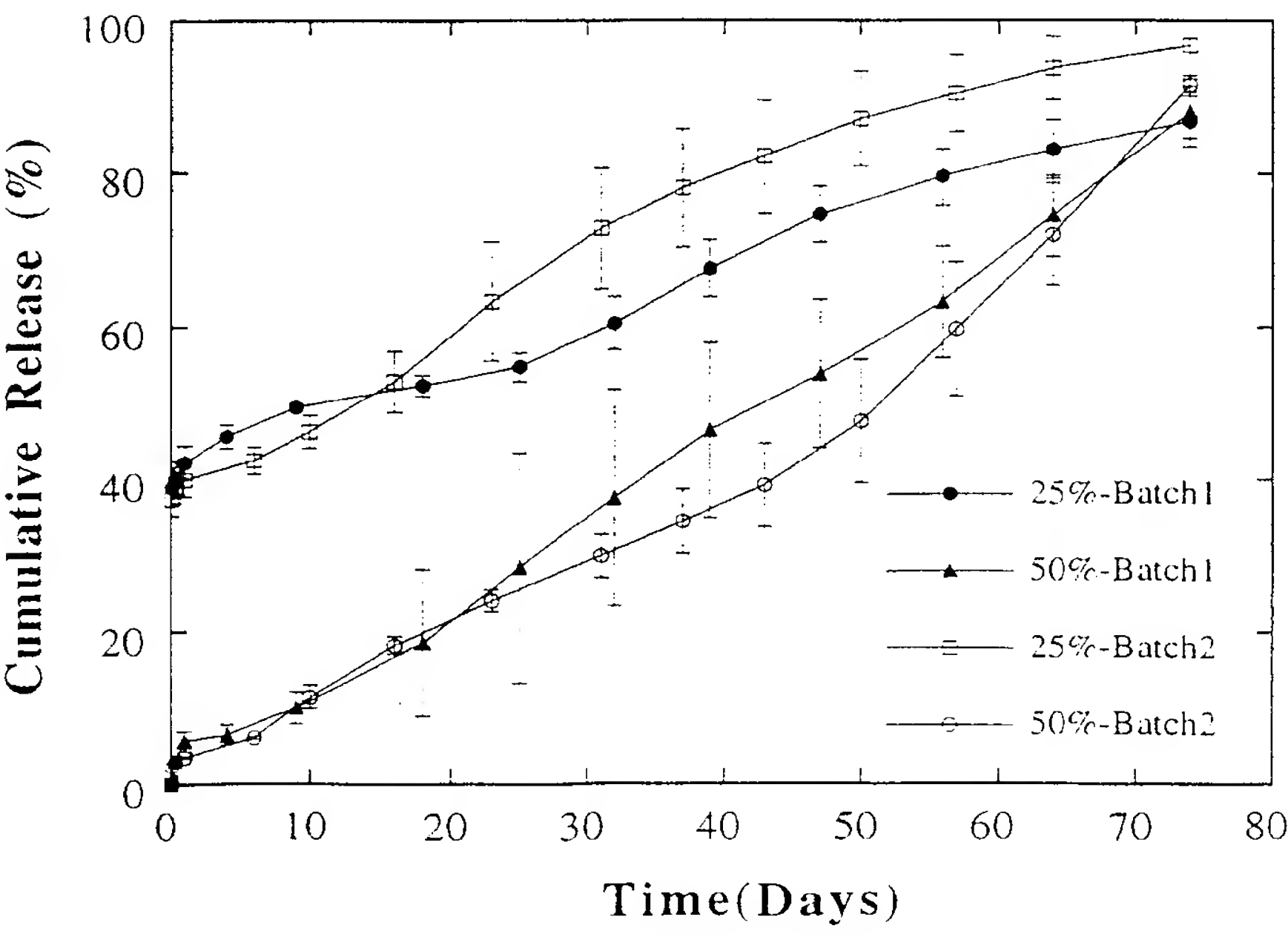
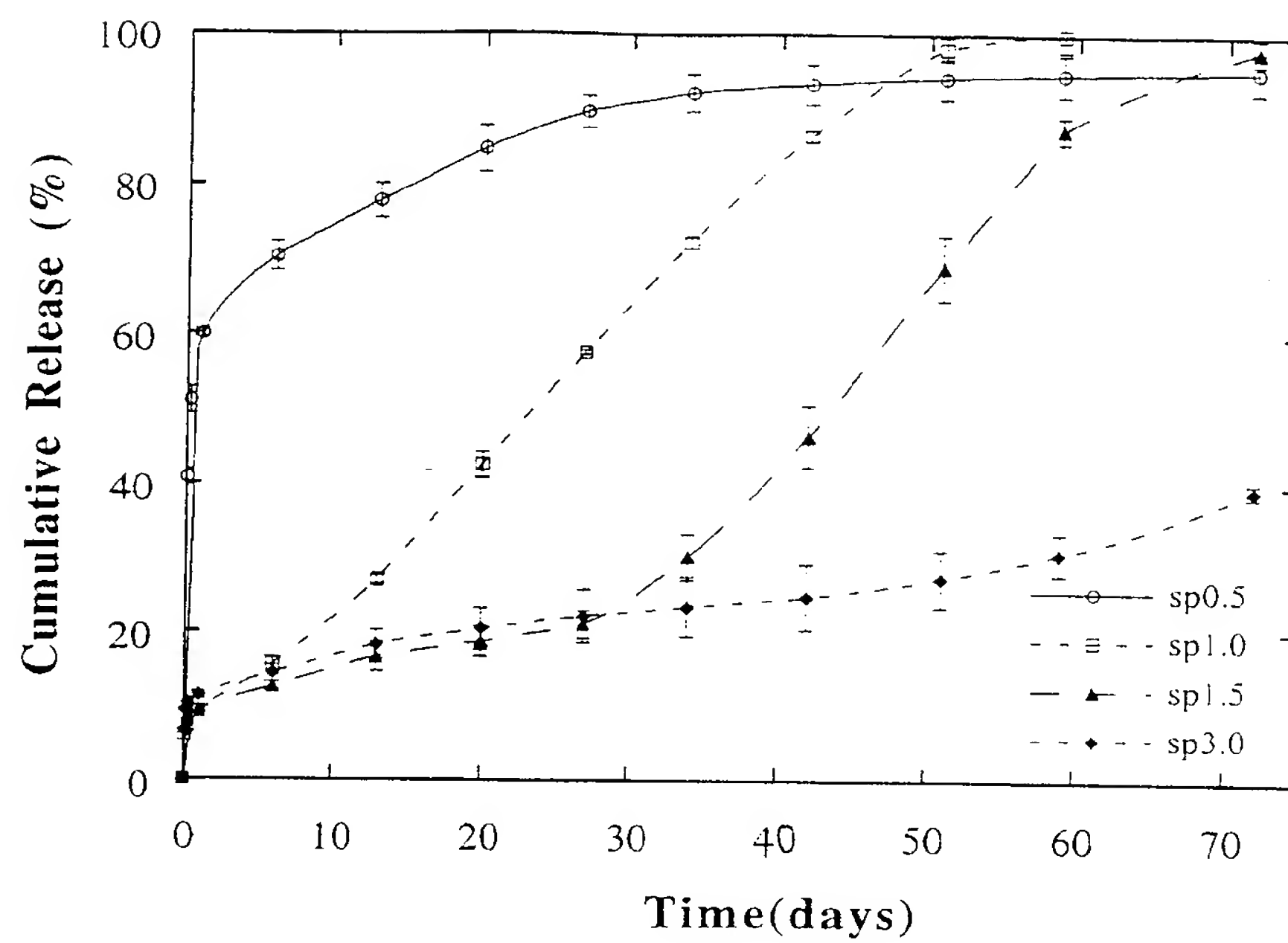
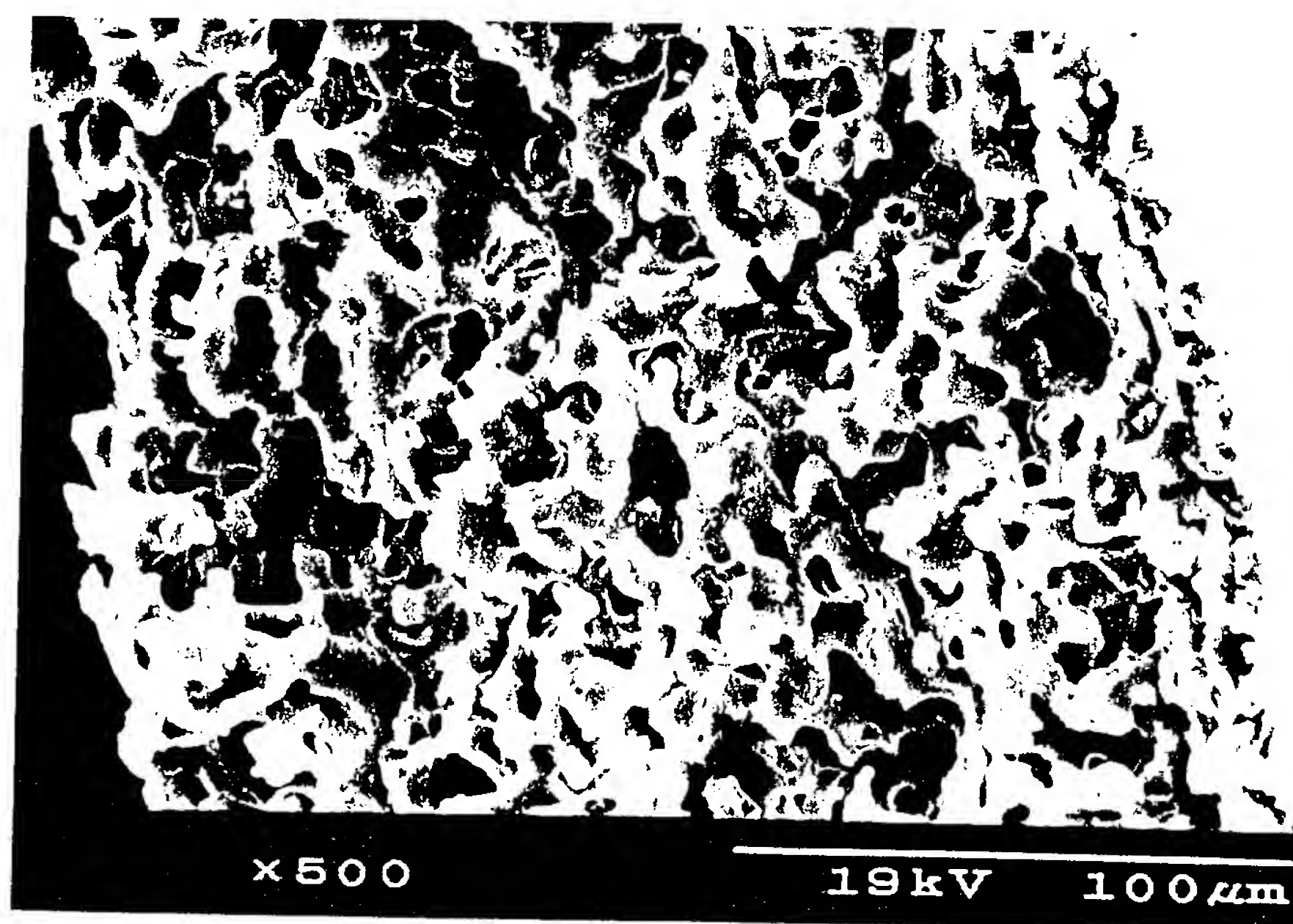


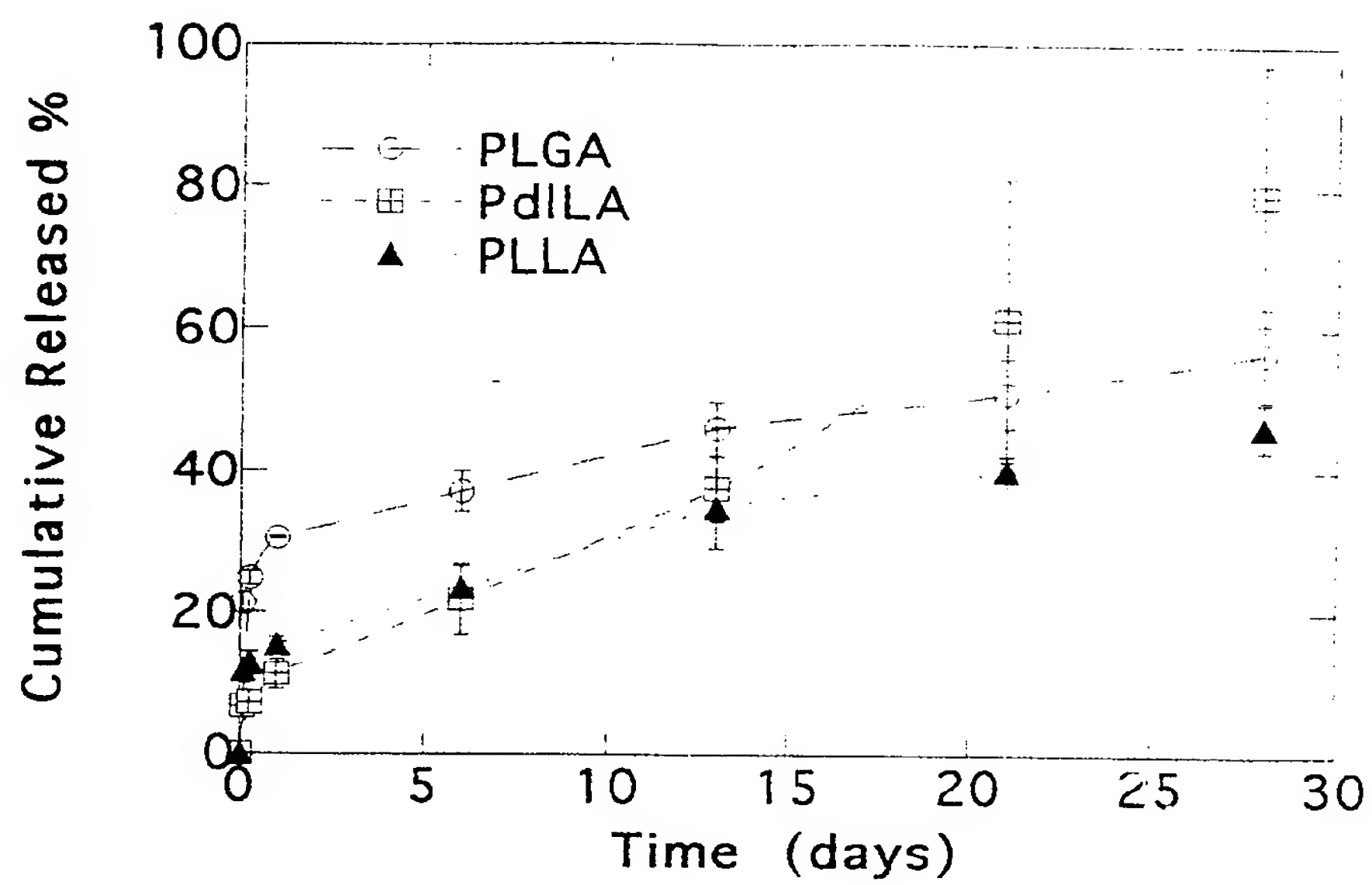
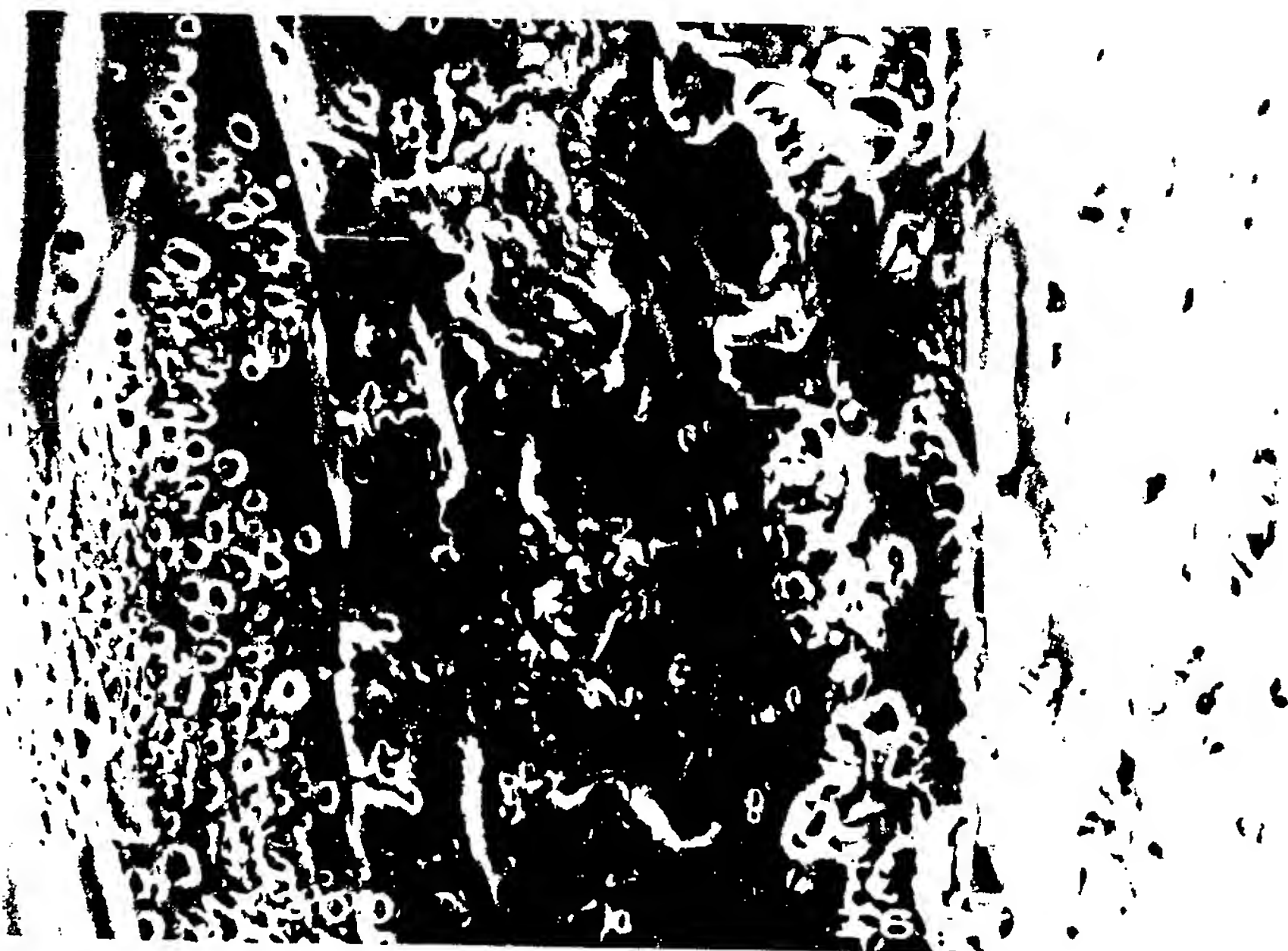
FIG.4



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FIG. 5**FIG. 6**

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FIG. 7**FIG. 8**

INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR 97/00289

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁶: A 61 K 9/19, 9/70, 47/34, 47/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁶: A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 371 516 A (GREGORY G.K.E. et al.) 01 February 1983 (01.02.83), abstract; claims 1,2,4; examples 5,9-11; column 3, line 68 - column 4, line 7;	1,3,4
Y	claim 1; column 3, line 68 - column 4, line 7.	2,5,7
Y	US 4 818 542 A (DE LUCA P.P. et al.) 04 April 1989 (04.04.89), claims 1-9,15-17,24,25; example 1; column 7, line 53 - column 8, lines 24-33.	2,5,7
X	US 4 305 502 A (GREGORY G.K.E. et al.) 15 December 1981 (15.12.81), abstract; column 2, line 53 - column 3, line 8; column 3, lines 21-47; examples 1,5,6,7.	1,3,4,7
A	EP 0 159 237 A1 (LABORATOIRE L. LAFON) 23 October 1985 (23.10.85), claims 1,7; page 12, line 5 - page 13, line 16; examples 1,2,5.	1,3
A	DE 24 23 811 A (KOHJIN CO., LTD.) 05 December 1974 (05.12.74), claims 1-3.	1,3

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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Date of the actual completion of the international search

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Name and mailing address of the ISA/ AT

AUSTRIAN PATENT OFFICE
Kohlmarkt 8-10
A-1014 Vienna
Facsimile No. 1/53424/535

Authorized officer

Mazzucco

Telephone No. 1/53424/437

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